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ORIGINAL ARTICLE

Positive remodeling is associated with more plaque vulnerability and higher frequency of plaque prolapse accompanied with post-procedural cardiac enzyme elevation compared with intermediate/negative remodeling in patients with acute myocardial infarction

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Summary
Background: We assessed the impact of remodeling patterns on pre- and post-procedural intravascular ultrasound (IVUS) findings and cardiac enzyme elevation after stenting in 310 acute myocardial infarction (AMI) patients.
Methods: The positive remodeling (PR) (PR group, $n = 113$) was defined as remodeling index (lesion/reference external elastic membrane cross-sectional area) >1.05, intermediate remodeling (IR) as between 0.95 and 1.05, and negative remodeling (NR) as < 0.95 (IR/NR group, $n = 197$). IVUS findings included ruptured plaque (a cavity that communicated with the lumen with an overlying residual fibrous cap fragment),

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multiple ruptured plaques (different plaque ruptures separated by a >5-mm length of artery containing smooth lumen contours), thrombus (discrete intraluminal filling defects), and plaque prolapse (tissue extrusion through the stent strut at post-stenting). We compared pre- and post-procedural IVUS findings and cardiac-specific troponin I (cTnI) elevation after stenting according to the remodeling pattern.
Results: The plaque rupture (60% vs. 42%, $p = 0.004$), multiple plaque ruptures (22% vs. 14%, $p = 0.014$), and IVUS-detected thrombus (42% vs. 28%, $p = 0.012$) were more common in the PR group compared with the IR/NR group. Post-stenting plaque prolapse was observed more frequently (36% vs. 22%, $p = 0.008$), and cTnI was elevated more significantly after stenting in the PR group compared with the IR/NR group ($\triangle$cTnI; $+7.8 \pm 51.1$ ng/ml vs. $+0.9 \pm 41.1$ ng/ml, $p = 0.008$). Multivariate analysis showed that PR [odds ratio (OR) = 1.92; 95% CI 1.04—2.98, $p = 0.028$], plaque rupture (OR 1.98; 95% CI 1.16—3.45, $p = 0.025$), IVUS-detected thrombus (OR 2.30; 95% CI 1.22—3.98, $p = 0.008$), and plaque prolapse (OR 8.40; 95% CI 4.19—16.84, $p < 0.001$) were independently associated with post-stenting cTnI elevation.
Conclusions: AMI patients with PR have more plaque vulnerability and higher frequency of plaque prolapse accompanied by post-procedural cardiac enzyme elevation compared with AMI patients with IR/NR.

Introduction

Patterns of arterial remodeling during the course of plaque development have been shown to play a pivotal role in the progression of atherosclerosis [1—5]. In vivo assessment of lesion site remodeling using intravascular ultrasound (IVUS) is performed by comparing the vessel area of the lesion to the reference segment [6]. Arterial remodeling is a heterogeneous process ranging from positive remodeling (PR), which is usually responsible for acute coronary syndromes, to negative remodeling (NR) which is usually associated with stenoses in patients with stable angina [7,8]. Lesions are classified as PR because the lesion site external elastic membrane (EEM) cross-sectional area (CSA) is larger than the reference segment, and lesions are classified as NR because the lesion site EEM CSA is smaller than the reference segment.

Typical IVUS features of acute myocardial infarction (AMI) include PR, plaque rupture, thrombus, and either spotty or deep calcium within the minimum lumen site [9—16]. Several studies have reported that rupture of a vulnerable plaque and subsequent thrombus formation is the most important mechanism leading to an acute coronary syndrome [17,18]. So far, data on the pre-procedural IVUS plaque characteristics and post-procedural IVUS findings according to the remodeling pattern in patients with AMI are lacking. We used IVUS to assess the relation between remodeling pattern and pre- and post-procedural IVUS findings in AMI.

Methods

Study population

From January 9, 2001 to July 31, 2007, we identified a total of 310 patients with a first AMI who underwent pre-intervention IVUS within 24 h from symptom onset, were stented successfully, and had post-intervention IVUS imaging. We excluded patients with prior MI, stent thrombosis, in-stent restenosis lesion, coronary artery bypass graft failure, severe heart failure or cardiogenic shock, patients studied with IVUS more than 24 h after symptom onset, and patients in whom adequate IVUS images could not be obtained. All 310 infarct lesions were treated with stent implantation: 187 with drug-eluting stents [138 with sirolimus-eluting stents (Cypher stent, Cordis, Johnson and Johnson, Miami Lakes, FL, USA) and 49 with paclitaxel-eluting stents (Taxus stent, Boston Scientific, Boston, MA, USA)], and 123 with bare metal stents.

The presence of ST-segment elevation MI was determined by >30 min of continuous chest pain, a new ST-segment elevation $\geq$2 mm on at least two contiguous electrocardiographic leads, and creatine kinase-MB >3 times normal. The presence of non-ST-segment elevation MI was diagnosed by chest pain and a positive cardiac biochemical marker without new ST-segment elevation. Infarct-related arteries were identified using a combination of electrocardiographic findings, left ventricular wall motion abnormalities on left

ventricular angiogram or two-dimensional echocardiogram, and coronary angiogram. The protocol was approved by the institutional review board. Hospital records of patients were reviewed to obtain information on clinical demographics.

Laboratory analysis

Venous blood samples were obtained within 24 h after stenting. The blood samples were centrifuged, and serum was removed and stored at −70 °C until the assay could be performed. Cardiac-specific troponin I (cTnI) levels were measured by a paramagnetic particle, chemiluminescent immunoenzymatic assay (Beckman, Coulter Inc., Fullerton, CA, USA). The serum levels of total cholesterol, triglyceride, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were measured by standard enzymatic methods. High-sensitivity C-reactive protein was analyzed turbidimetrically with sheep antibodies against human C-reactive protein; this has been validated against the Dade-Behring method [19].

Quantitative coronary angiography (QCA) analysis

Coronary angiogram was analyzed with validated QCA system (Philips H5000 or Allura DCI program, Philips Medical Systems, Eindhoven, the Netherlands). With the outer diameter of the contrast-filled catheter as the calibration standard, the minimal lumen diameter and reference diameter were measured in diastolic frames from orthogonal projections.

IVUS imaging and analysis

All IVUS examinations were performed before and after stenting after intracoronary administration of 300 μg nitroglycerin using a commercially available IVUS system (Boston Scientific Corporation/SCIMed, Minneapolis, MN, USA). The IVUS catheter was advanced distal to the target lesion, and imaging was performed retrograde to the aorto-ostial junction at an automatic pullback speed of 0.5 mm/sec.

IVUS analysis was performed according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acqusition, Measurement and Reporting of Intravascular Ultrasound Studies [6]. EEM and lumen CSAs were measured. Plaque plus media (P&M) CSA was calculated as EEM minus lumen CSA; and plaque burden was calculated as P&M divided by EEM CSA. Proximal and distal references were the single slices with the largest lumen and smallest plaque CSAs within 10 mm proximally and distally, but before any large side branch. The lesion was the site with the smallest lumen CSA; if there were multiple image slices with the same minimum lumen CSA, then the image slice with the largest EEM and P&M was measured. Coronary artery remodeling was assessed by comparing the lesion site to the reference EEM CSA. Remodeling index was the lesion site EEM CSA divided by the average of the proximal and distal reference EEM CSA. PR was defined as a remodeling index >1.05, intermediate remodeling (IR) as a remodeling index between 0.95 and 1.05, and NR as a remodeling index <0.95 [20]. Hypoechoic plaque was less bright compared with the reference adventitia. Hyperechoic, noncalcified plaque was as bright as or brighter than the reference adventitia without acoustic shadowing. Calcium plaque was hyperechoic with shadowing. A calcified lesion contained >90° of circumferential lesion calcium. When there was no dominant plaque composition, the plaque was classified as mixed.

A ruptured plaque contained a cavity that communicated with the lumen with an overlying residual fibrous cap fragment. A fragmented and loosely adherent plaque without a distinct cavity and without a fibrous cap fragment was not considered a plaque rupture. Rupture sites separated by a length of artery containing smooth lumen contours without cavities were considered to represent different plaque ruptures [21,22]. Plaque cavity was measured and extrapolated to the ruptured capsule area. Thrombus was an intraluminal mass having a layered or lobulated appearance, evidence of blood flow (microchannels) within the mass, and speckling or scintillation [22,23]. A lipid-pool like image was defined as a pooling of hypoechoic or echolucent material covered with a hyperechoic layer.

At post-intervention, we measured the minimum stent CSA. Percent stent expansion was calculated as minimum stent CSA divided by mean reference lumen CSA. Plaque prolapse was defined as tissue extrusion through the stent strut at post-intervention.

Statistical analysis

The statistical Package for Social Sciences (SPSS) for Windows, version 15.0 (Chicago, IL, USA) was used for all analyses. Continuous variables were presented as the mean value ±1SD; comparisons were conducted by Student's *t*-test or nonparametric Wilcoxon test if normality assumption was violated. Discrete variables were presented as percentages and relative frequencies; comparisons were conducted by chi-square statistics or Fisher's

Table 1 Baseline characteristics.

	PR ($n = 113$)	IR/NR ($n = 197$)	p-value
Age (years)	62 ± 13	66 ± 11	0.043
Male gender	72 (64)	107 (54)	0.11
Clinical presentation			0.9
NSTEMI	68 (61)	117 (59)	
STEMI	45 (40)	80 (41)	
Diabetes mellitus	46 (41)	65 (33)	.17
Hypertension	89 (79)	151 (77)	0.7
Smoking	35 (31)	70 (36)	0.4
Family history of coronary artery disease	26 (23)	26 (13)	0.026
Glycoprotein IIb/IIIa inhibitors	26 (23)	34 (17)	0.2
Use of distal protection devices	13 (12)	11 (6)	0.060
Ejection fraction (%)	43 ± 13	46 ± 12	0.099
cTnI (ng/ml)	16.6 ± 47.4	14.4 ± 40.3	0.7
White blood cells ($10^3/mm^3$)	9.8 ± 4.1	8.8 ± 3.1	0.091
Hemoglobin (g/dl)	12.2 ± 2.2	12.3 ± 2.1	0.8
Platelet count ($10^3/mm^3$)	243 ± 89	222 ± 85	0.12
Creatinine clearance (ml/min)	60 ± 36	64 ± 31	0.3
Total cholesterol (mg/dl)	172 ± 47	168 ± 43	0.6
Triglyceride (mg/dl)	136 ± 49	125 ± 71	0.2
LDL-cholesterol (mg/dl)	105 ± 42	102 ± 37	0.6
HDL-cholesterol (mg/dl)	42 ± 12	43 ± 14	0.3
High-sensitivity C-reactive protein (mg/dl)	2.4 ± 5.4	1.9 ± 3.4	0.5

Data are n (%), or mean $\pm$ SD. PR, positive remodeling; IR/NR, intermediate remodeling/negative remodeling; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; cTnI, cardiac-specific troponin I; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

exact test as appropriate. Multivariate analysis was performed to identify independent predictors of post-stenting cTnI elevation. Univariate analyses were first conducted to identify potential risk factors for post-stenting cTnI elevation. The likelihood ratio test was used, and the variables with a p-value of < 0.2 were included in the multivariate model. Finally, a stepdown logistic regression was performed. The least significant variable was dropped at each step until only covariates with a p-value < 0.05 remained. A p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

The baseline characteristics are summarized in Table 1. The PR group was younger and had more family history of coronary artery disease compared with the IR/NR group. There were trends toward more frequent use of distal protection devices, lower ejection fraction, and higher white blood cell counts in the PR group compared with the IR/NR group.

Angiographic and procedural results

Angiographic findings and procedural results are summarized in Table 2. Although there were no significant differences in infarct-related arteries, lesion location, number of diseased vessels, Thrombolysis In Myocardial Infarction (TIMI) flow grade, used stent types, and stent diameter and length between the PR group and the IR/NR group, angiographic lesion length was significantly longer and inflation pressure for stent implantation was significantly higher in the PR group compared with the IR/NR group. There was a strong trend toward increased PR when paclitaxel-eluting stents were used, compared with sirolimus-eluting or bare-metal stents [paclitaxel-eluting stent, 19/49 (39%); sirolimus-eluting stent, 35/138 (25%); bare-metal stent, 31/123 (25%); $p = 0.15$)].

IVUS results

IVUS findings are summarized in Table 3. Lesion site EEM CSA, P&M CSA, and plaque burden were significantly greater in lesions with PR compared with lesions with IR/NR. IVUS lesion length was significantly longer, and calcium arc was signifi-

Table 2 Coronary angiographic findings and procedural results.

	PR ($n = 113$)	IR/NR ($n = 197$)	p-value
Infarct-related artery			0.12
Left main	3 (3)	2 (1)	
Left anterior descending artery	54 (48)	113 (57)	
Left circumflex artery	13 (12)	29 (15)	
Right coronary artery	43 (38)	53 (27)	
Lesion location			0.096
Ostium	1 (1)	3 (2)	
Proximal	37 (33)	84 (43)	
Middle	67 (59)	88 (45)	
Distal	8 (7)	22 (11)	
Multivessel disease	54 (48)	100 (51)	0.4
TIMI flow grade 0	23 (20)	35 (18)	0.5
Stent type			0.17
Sirolimus-eluting stent	53 (47)	85 (43)	
Paclitaxel-eluting stent	12 (11)	37 (19)	
Bare-metal stent	48 (43)	75 (38)	
No. of deployed stents	1.25 ± 0.53	1.16 ± 0.38	0.13
Stent diameter (mm)	3.31 ± 0.50	3.22 ± 0.41	0.10
Stent length (mm)	24.9 ± 11.6	23.6 ± 10.4	0.3
Inflation pressure (mmHg)	14.8 ± 2.7	14.2 ± 2.8	0.039
Reference diameter (mm)	3.26 ± 0.89	3.32 ± 0.75	0.5
Pre-MLD (mm)	0.63 ± 0.32	0.65 ± 0.51	0.7
Lesion length (mm)	21 ± 10	18 ± 8	0.031

Data are n (%), or mean $\pm$ SD. PR, positive remodeling; IR/NR, intermediate remodeling/negative remodeling; TIMI, thrombolysis in myocardial infarction; MLD, minimal lumen diameter.

Table 3 Intravascular ultrasound findings.

	PR ($n = 113$)	IR/NR ($n = 197$)	p-value
Reference			
EEM CSA (mm^2)	12.3 ± 4.5	13.2 ± 4.8	0.13
Lumen CSA (mm^2)	8.3 ± 3.2	9.0 ± 3.0	0.11
P&M CSA (mm^2)	4.0 ± 2.2	4.2 ± 2.8	0.6
Plaque burden (%)	32 ± 12	32 ± 11	1.0
Lesion site			
EEM CSA (mm^2)	14.6 ± 5.0	11.3 ± 3.9	<0.001
Lumen CSA (mm^2)	2.6 ± 1.6	2.4 ± 1.0	0.7
P&M CSA (mm^2)	12.0 ± 4.5	8.9 ± 3.9	<0.001
Plaque burden (%)	82 ± 36	76 ± 30	0.014
IVUS lesion length (mm)	26 ± 16	22 ± 12	0.026
Calcium arc (°)	97 ± 106	150 ± 106	<0.001
Lipid-pool like image	45 (40)	51 (26)	0.011
Scattered calcification	70 (62)	81 (41)	<0.001
Plaque morphology			<0.001
Hypoechoic	72 (64)	80 (41)	
Hyperechoic, non-calcified	21 (19)	31 (16)	
Hyperechoic, calcified	12 (11)	66 (34)	
Mixed	8 (7)	20 (10)	
Remodeling index	1.20 ± 0.18	0.88 ± 0.13	<0.001
Minimum stent CSA (mm^2)	7.92 ± 2.64	7.75 ± 2.56	0.079
Stent expansion (%)	95 ± 22	86 ± 29	0.034

Data are n (%), or mean $\pm$ SD. PR, positive remodeling; IR/NR, intermediate remodeling/negative remodeling; EEM, external elastic membrane; CSA, cross-sectional area; P&M, plaque plus media; IVUS, intravascular ultrasound.

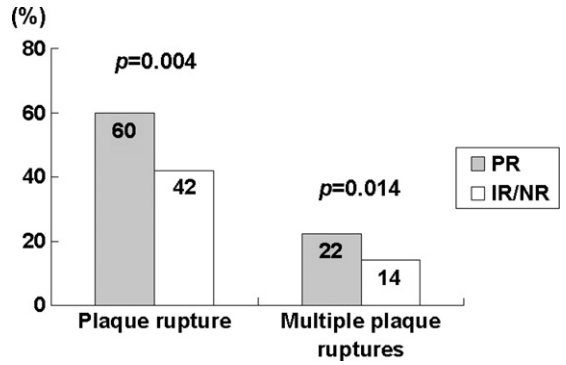

Fig. 1 The incidence of plaque rupture and multiple plaque ruptures in lesions with positive remodeling (PR) vs. lesions with intermediate remodeling (IR)/negative remodeling (NR).

cantly smaller in lesions with PR compared with lesions with IR/NR. The presence of lipid-pool like image, scattered calcification, and hypoechoic plaque were significantly more common in lesions with PR compared with lesions with IR/NR. Percent stent expansion was significantly greater in lesions with PR compared with lesions with IR/NR.

Plaque rupture and multiple plaque ruptures were observed more frequently in lesions with PR compared with lesions with IR/NR (Fig. 1). Plaque cavity CSA was significantly greater and ruptured plaque length was significantly longer in lesions with PR compared with lesions with IR/NR (Fig. 2). IVUS-detected thrombus was observed more frequently in lesions with PR compared with lesions with IR/NR (Fig. 3). At post-intervention, plaque prolapse was observed more frequently in lesions with PR compared with lesions with IR/NR (Fig. 4).

Post-stenting cTnI elevation

Overall, cTnI was elevated after stenting in 179 patients (58% of the enrolled patients). cTnI was more significantly elevated after stenting in patients with PR compared with patients without IR/NR (ΔcTnI; $+7.8 \pm 51.1$ ng/ml vs. $+0.9 \pm 41.1$ ng/ml, $p = 0.008$). Multiple logistic regression analysis was performed to determine independent predictors of post-stenting cTnI elevation. The following variables were tested (all with $p < 0.2$ in univariate analysis): male gender, diabetes mellitus, TIMI flow grade 0, stent length, IVUS plaque burden at the minimum lumen sites, plaque rupture, IVUS-detected thrombus, PR, plaque prolapse, and percent stent expansion. PR [odds ratio (OR) 1.92; 95% confidence interval

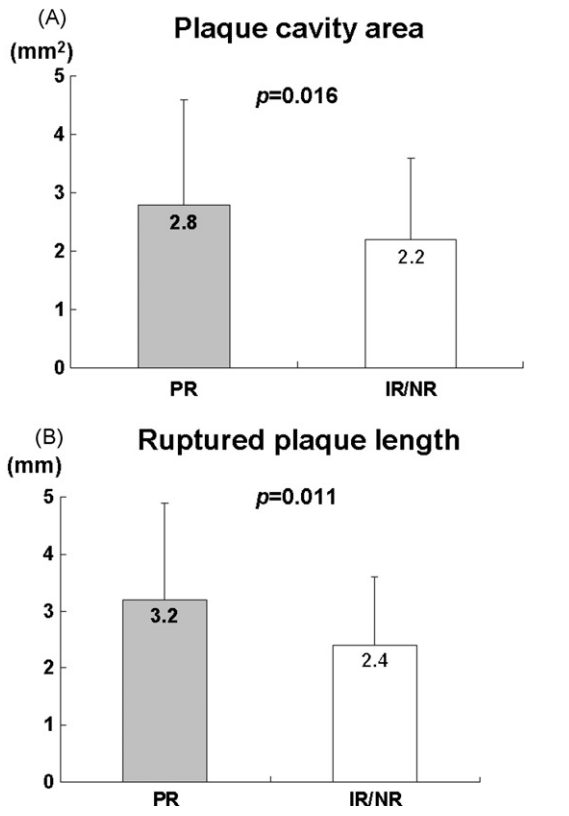

Fig. 2 Plaque cavity area (A) and ruptured plaque length (B) in lesions with positive remodeling (PR) vs. lesions with intermediate remodeling (IR)/negative remodeling (NR).

(CI) 1.04—2.98, $p = 0.028$], plaque rupture (OR 1.98; 95% CI 1.16—3.45, $p = 0.025$), IVUS-detected thrombus (OR 2.30; 95% CI 1.22—3.98, $p = 0.008$), and plaque prolapse (OR 8.40; 95% CI 4.19—16.84, $p < 0.001$) were independently associated with post-stenting cTnI elevation.

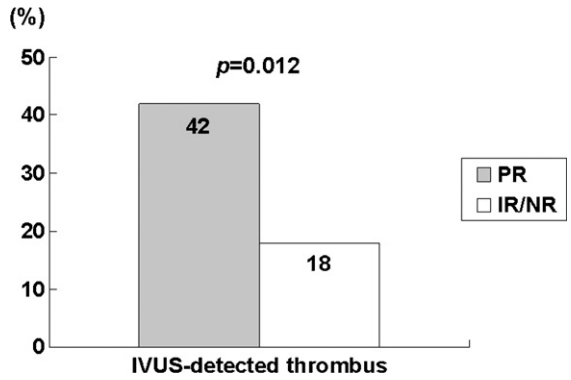

Fig. 3 The incidence of intravascular ultrasound (IVUS)-detected thrombus in lesions with positive remodeling (PR) vs. lesions with intermediate remodeling (IR)/negative remodeling (NR).

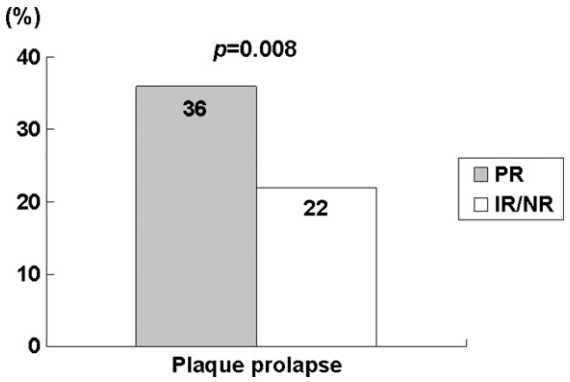

Fig. 4 The incidence of post-stenting plaque prolapse in lesions with positive remodeling (PR) vs. lesions with intermediate remodeling (IR)/negative remodeling (NR).

Discussion

The present IVUS study demonstrated that AMI patients with PR had: 1) greater lesion site plaque burden, longer lesion length, and less severe calcification; 2) more lipid-pool like image, more scattered calcification, and more hypoechoic plaque; 3) greater percent stent expansion; 4) more plaque rupture and multiple plaque ruptures and more IVUS-detected thrombus; 5) more post-stenting plaque prolapsed; and 6) more significant cTnI elevation after stenting. Therefore, AMI patients with PR have more plaque vulnerability and higher frequency of plaque prolapse accompanied by more post-procedural myonecrosis compared with AMI patients with IR/NR.

Coronary arteries respond to plaque growth by either outward expansion of the vessel wall (PR) [1,2] or vessel shrinkage (NR) [3—5]. Several studies have suggested that lesions with PR may be both beneficial (avoiding luminal stenosis) and harmful (promoting plaque vulnerability) [8,24,25]. In contrast, lesions with NR may be associated with significant stenoses [5,26], but may appear more stable. Lesions with PR are also associated with higher long-term target lesion revascularization after nonstent interventional procedures [27], restenosis after bare-metal stent implantation [28—31], and drug-eluting stent implantation [32].

Autopsy studies have suggested that AMI results from spontaneous plaque rupture or erosion and subsequent thrombosis [33,34]. Several IVUS studies have reported varying percentage of culprit-lesion plaque rupture in patients with acute coronary syndrome [35—37]. Plaque ruptures tend to occur at a point where the fibrous cap is thinnest and most heavily infiltrated by macrophages indicating ongoing inflammation at the site of plaque disruption [38]. Pathological studies have shown that coronary artery plaques with PR have a higher lipid content and macrophage count which are recognized histological markers for plaque vulnerability [39—41]. In the present study, lesions with PR have more plaque rupture, more multiple plaque ruptures, more IVUS-detected thrombus, more hypoechoic plaque, more lipid-pool like images, and more spotty calcification compared with lesions with IR/NR. The results of the present study are consistent with previous pathological and IVUS studies in which PR may make the plaque more vulnerable to rupture and cause AMI.

Plaque prolapse is an intraluminal tissue extrusion through stent struts and this can be easily and frequently detected by IVUS. It has been known that several pre-intervention IVUS features such as hypoechoic plaque rather than fibrous or calcified plaque, smaller minimal lumen diameter, and a larger plaque burden were associated with plaque prolapse, and the risk of plaque prolapse was higher during aggressive stenting procedure [35,36]. Our previous study showed that the incidence of plaque prolapse after stenting for infarct-related artery was 27% and pre-intervention IVUS lesion characteristics — plaque rupture and PR — and longer stent length predict plaque prolapse [42]. In the present study, plaque prolapse was observed more frequently in lesions with PR compared with lesions with IR/NR. Vulnerable plaques like PR and plaque rupture may provide the conditions for tissue extrusion through the stent struts.

Previous studies demonstrated that cardiac enzyme elevation after percutaneous coronary intervention is associated with higher mortality [43—47]. Cardiac enzyme elevation after coronary artery intervention is related to the large plaque burden and unstable plaque morphometry [48—50]. In addition to these pre-intervention IVUS findings, more aggressive stenting procedures appeared to be associated with greater levels of cardiac enzyme elevation [43,50—52]. In the present study, pre-intervention IVUS findings — PR, plaque rupture, IVUS-detected thrombus — and post-intervention plaque prolapse were independently associated with cTnI elevation after stent implantation. The results of the present study suggest that aggressive stenting with high pressure inflation for lesions with vulnerable plaque like PR, plaque rupture, and thrombus should be avoided to prevent post-stenting myonecrosis in patients with AMI because plaque prolapse is associated with aggressive stenting procedures and post-stenting cardiac enzyme elevation [35,42].

Study limitations

First, the present study is retrospective single-center study, so, is subject to limitations inherent in this type of clinical investigation. Second, IVUS imaging was performed at the discretion of the individual operators leading to potential selection bias. Third, it may be difficult to differentiate between an organized thrombus and plaque prolapse. IVUS data were analyzed by 2 independent observers (H.Y.J and C.Y.H). The presence of plaque prolapse was confirmed when 2 independent observers agreed. However, if so, it is possible that some cases identified as having plaque prolapse actually had thrombus prolapse. Fourth, volumetric IVUS analysis was not performed in the present study. Fifth, we excluded the patients with serious conditions such as severe heart failure, cardiogenic shock, and coronary artery bypass graft failure. Thus, the present study might not represent the whole spectrum of AMI patients. Sixth, long-term clinical follow-up was not available.

Conclusions

AMI patients with PR have more plaque vulnerability (more plaque rupture, more multiple plaque ruptures, and more IVUS-detected thrombus) and higher frequency of post-stenting plaque prolapse accompanied by more post-procedural cardiac enzyme elevation compared with AMI patients with IR/NR.

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